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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,185	02/20/2002	Stanley T. Crooke	ISIS-5030	7585

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,185	CROOKE, STANLEY T.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/08/04, 1/10/05, 1/20/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,40-58,61-71 and 74-95* is/are pending in the application.

4a) Of the above claim(s) *88-92,94 and 95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37,40-58,61-71,74-87 and 93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/23/02,12/05/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I in the reply filed on 10/06/04 is acknowledged. The traversal is on the ground(s) that the Office has failed to identify any "different steps" that would be required using a single stranded polynucleotide versus a method using a double stranded polynucleotide. This is not found persuasive because it is the examiners position that the step in the different methods that would clearly be different would be the administration of a single stranded oligonucleotide, versus the administration of a double stranded oligonucleotide, for example.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-37, 40-58, 61-71, and 74-95 are pending.

Claims 88-92, 94 and 95 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/08/04.

Claims 1-37, 40-58, 61-71, 74-87, and 93 are under examination. It is noted that claim 93 was inadvertently ignored in the restriction requirement of 10/06/04 but clearly belongs in the elected group and is under examination.

Applicant filed a preliminary amendment on 1/20/05 which deleted priority claims. Based on the preliminary amendment, the instant application has an effective filing date of 7/06/01.

At page 2, line12, the specification refers to US patent "6,017,094", but it appears that applicant mistyped the patent number and intended to refer to US patent "6,107,094".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 8-11, 13, 14, 33-37, 40-45, 51-58, 61-71, 74-79, 84-86, and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al [Journal of Biological Chemistry, Vol. 273(5):2532-2542, 1/30/98].

Wu et al disclose the administration of single stranded RNA and RNA-like oligonucleotides, targeted to Ha-ras, to human T4 human bladder carcinoma cells to inhibit Ha-ras expression. It is noted that the instant specification asserts that the RNase III of the invention is ubiquitously expressed in human tissues and cell lines (see page 6 of the specification). The prior art therefore has met the method steps of the invention since a single stranded RNA oligonucleotide is administered to cells that inherently

contain RNase III and as disclosed in the instant specification and the Wu reference RNAse III is located in the nucleus and that RNase III causes cleavage of a RNA oligonucleotide/target complex. Claim 8 is rejected in so far as there is no apparent difference between the purified RNase of claim 8 and the endogenous RNase III of/in the cell contacted in the context of the claim. Figure B of Wu et al discloses that the oligonucleotides range from full RNA oligonucleotides to full 2'methoxy oligonucleotides with various gapmer combinations in between where phosphorothioate linkages are used. Claim 54 is rejected in so far as the context of "forms outside the cell" is reasonably considered a latent characteristic of the oligonucleotide since the language is passive and not necessarily active, for example.

Claims 12, 54, and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Fire et al [US 6,506,559].

Fire et al disclose in claims 1 and 6, for example the administration of a double stranded RNA (ie formed outside of a cell) to an cell (which includes, for example rat and human cells, see column 8, for example) where the double stranded RNA corresponds to a gene whose expression is to be inhibited.

Claims 1-5, 9-11, 13, 14, 33-37, 40-45, 51-53, 55-58, 61-71, 74-79, 84-86 and 93 are rejected under 35 U.S.C. 102(a) as being anticipated by Crooke [US 6,107,094].

Claim 2 of 6,107,094 is a method that includes the steps of introducing into an organism, and hence to cell within, an oligomeric compound having a sequence of nucleoside subunits that are modified and has a plurality of 2'-hydroxy-pentofuranosyl sugar moieties. The method therefore includes the introduction of introducing an RNA-like oligomer (see Figure 1, for example). The method is for dsRNase activation and a ds RNase of the invention is found in human T24 cells. The specification discloses the introduction of the RNA and RNA-like oligomers of Figure 1 which are oligonucleotides that range from full RNA oligonucleotides to full 2'methoxy oligonucleotides with various gapmer combinations in between where phosphorothioate linkages are used, which are targeted to Ha-ras to inhibit Ha-ras via a dsRNase. See column 15-17, for further example of RNA oligomers to be administered to elicit dsRNase activity in various organisms and therein it is also disclosed. The prior art meets all of the method steps of the instantly claimed methods.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 9-11, 13, 14, 33-37, 40-45, 51-53, 55-58, 61-71, 74-79, 84-86 and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,107,094. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention of claim 2 of '094 embraces the methods of the instant claims. The method of '094 is directed to activating an RNase via the administration of an oligomer that comprises a plurality of 2'-hydroxy-pentofuranosyl sugar moieties. The method of the instant claims are drawn to methods that comprise the administration of RNA and RNA-like oligomers to inhibit gene expression via dsRNase activation. The specification of '094 clearly indicates that the oligomers considered in the method of claims 2 are the same oligomers shown exemplified in the instant specification (compare Figure 1 if each application, for example) or it would have been obvious to use the oligomers of the instant invention based on the teachings of Wu et al above, for example, since the teachings of Wu et al are also the same Ha-ras oligomers for inhibiting a target RNA expression via a dsRNase activation (see Figure 1 of Wu et al).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-37, 40-58, 61-71, and 74-87, and 93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 2 which corresponds to the human RNase III protein. The specification also provides a description of a few yeast and a bacterial an a *C.elegans* RNase III proteins. However, the claims are directed to encompass the use of corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth (see pages 7-10 of the specification, for example). None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. The specification, for example, shows that the exemplified human RNase III has 41% identity with *C.elegans* 15-17% identity with yeast and 16% homology with E.coli RNase III.. It is stated at page 6 of the specification is substantially larger and comprises more domains than the above RNase III's. The claimed invention requires the use of a vast range of RNase III protein or

RNase III domains. Applicant specification and the prior art describe but a few. The claimed methods require the contacting of a RNA-like /target complex with and RNAse II polypeptide or RNase III containing polypeptide or the addition of such polypeptides to a cell.

The claims also require the "enrichment" or overexpression of RNase III in cells as well as methods that require the administration of the protein to cell. One in the art clearly requires a description of a sufficient number of RNases in order to introduce them via directly to a cell or by nucleic acid transformation (ie requiring a nucleic acid sequence coding for the RNase III). One in the art would require, also for example a description or structure of compounds that may increase or cause overexpression or RNAse III (see page 35, for example). The specification asserts that overexpression can be effected by manipulation of cells. The specification fails to provide and adequate description of any moieties that may be used to effect such manipulation, for example.

The instant claims are drawn to "modification" of a target RNA. The specification asserts that to "modify" includes an enzyme [RNase III] that may "modify" its RNA substrate by binding and interfering with the function of the RNA, but not cleave it; or may bind and cleave (see page 9). The specification provides the structure of a limited number of RNAse III species that may bind and cleave an RNA/target complex and provides no examples of binding and interfering with no cleavage (see page 9 of the specification, for example). What is the structure of those enzymes that function in such a manner, for example? The invention also includes the use of polypeptides[RNase III] that retain nuclease activity but without specificity for an RNA/RNA duplex (claims 33-

40, 42, 44, 45-50, 61, 65, 67-71, and 74 do not require that the complex contain an RNA or RNA-like oligomer to bind the target RNA (and also see page 9, line22-26)). What is the structure of a dsRNase III that cleaves a DNA/target RNA? It is noted that claims 55-58 do not even require the use of an RNA, RNA-like oligo, or even a polynucleotide but an "agent". What is the structure of an "agent" that allows for its use in targeting by a dsRNase III, or, for example, the structure of an RNAse III that generically cleaves or binds to or recognizes an "agent"/ target complex such that a gene is inhibited from being expressed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were

found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an

adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The species specifically disclosed are not representative of the genus because the genus is highly variant.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Prior art, Agrawal et al [WO 94/01550], is made of record and not relied upon, but is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
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Art Unit 1635